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RESEARCH ARTICLE

An efficient synthesis of (NH)-phenanthridinones *via* ligand-free copper-catalyzed annulation†

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An efficient and concise procedure for the ligand-free copper-catalyzed cascade reaction of C–O and C–N bond coupling was developed, which afforded various (NH)-phenanthridinones in moderate to good yields with tolerance of a wide variety of substrates. This method could be useful for the syntheses of natural alkaloids.

Introduction

Phenanthridinone is an important building block for organic synthesis because it has been frequently discovered in a wide variety of natural alkaloids[1] and in addition possesses several types of bioactivity such as antilymphoma, antileukemia, antitumor, antiviral and inhibitor of HIV-1 integrase *etc*.[2] Traditional approaches for the syntheses of phenanthridinones are *via* intramolecular annulation of the corresponding aminocarboxylatebiphenyls[3] or the reductive cyclization of nitrocarbonylbiphenyls.[4] Other common strategies include radical cyclization,[5] Schmidt reaction/electrophilic aromatic substitution of biphenylcarboxylic acids,[6] Beckmann rearrangement of fluorenones,[7] microwave-assisted anionic ring closure reaction,[8] anionic cycloaromatization of 1-aryl-3-hexen-1,5-diynes,[9] oxidative coupling reaction of *N*-arylbenzamide[10] and Pd-catalyzed annulation of aryne with *o*-halobenzamides.[11]

In recent years, palladium-catalyzed C–H functionalization has been well developed and used as a powerful method for carbon–carbon[12] and carbon–heteroatom[13] bond formation. Development toward the syntheses of phenanthridinones has also turned to palladium-catalyzed C–H bond activation. In particular, the palladium catalytic cyclization reactions of *N*-aryl-2-bromobenzamide[14] and *N*-arylbenzamide[15] are often reported. Domino processes for multiple C–H bond activations were also carried out by Wang[16] and Cheng's[17] research groups. However, these domino reactions were restricted to the synthesis of *N*-methoxyphenanthridinones and further photochemical reaction was required to provide the corresponding (NH)-phenanthridinones for other synthetic applications.

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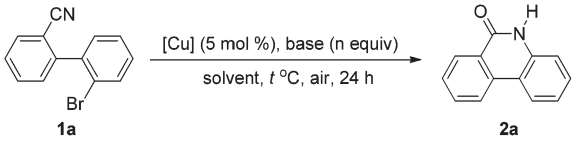
Very recently, novel procedures for the synthesis of phenanthridinones through an oxidative insertion of carbon monoxide to 2-aminobiaryls were disclosed independently by Orito, Zhu and Chuang.[18] Their protocols selectively provide different sort of phenanthridinones. However, only one case among these reports is related to the synthesis of (NH)-phenanthridinones. Therefore, the development of novel methods to address this issue is still desirable. Our experience in catalytic coupling reactions involving nitriles[19] encouraged us to explore the possibility of the synthesis of free (NH)-phenanthridinones by a coupling reaction involving a nitrile. Herein, we report the first example of an efficient and convenient synthetic pathway to form (NH)-phenanthridinones through a copper-catalyzed cyclization reaction involving C–O and C–N bond coupling of a nitrile.

Results and discussion

Our initial studies used 2′-bromo-[1,1′-biphenyl]-2-carbonitrile (**1a**) as a model substrate (Table 1, entry 1), which was treated with 5 mol% CuI and 3 equiv. of NaOH in 1.0 mL *t*BuOH at 120 °C for 24 h; and the corresponding phenanthridinone (**2a**) was obtained in 69% NMR yield. Product **2a** was confirmed by ^{1}H NMR, ^{13}C NMR and HRMS analysis. We also observed a small amount of undefined side products and biphenylamide after working up the reaction.

To optimize the reaction conditions, the effect of solvent, base, reaction temperature and copper source were investigated (Table 1). We first examined the copper source for this reaction (entries 2–4). Among the various copper sources employed, CuI was found to be the most effective catalyst, providing the desired product **2a** in 69% NMR yield (entry 1). Screening of the base revealed that NaOH and KOH gave similar results (entries 1 and 5). The cyclization reaction could not be completed within 24 h when using LiOH as base (entry 6). The use of a NaO*t*Bu–H_2O system (entry 7) also afforded the

Table 1 Optimization of reaction conditions[a]



Entry	[Cu]	Base (*n*)	Solvent	Temp (°C)	Yield[b] (%) 1a	2a
1	CuI	NaOH (3)	*t*BuOH	120	0	69
2	CuBr	NaOH (3)	*t*BuOH	120	0	54
3	Cu_2O	NaOH (3)	*t*BuOH	120	0	62
4	$Cu(OAc)_2$	NaOH (3)	*t*BuOH	120	0	49
5	CuI	KOH (3)	*t*BuOH	120	0	66
6	CuI	LiOH (3)	*t*BuOH	120	6	52
7	CuI	NaO*t*Bu (4)–H_2O (1.1)	*t*BuOH	120	23	35
8	CuI	NaOH (4)	*t*BuOH	120	0	87
9	CuI	NaOH (4)	*t*BuOH	140	0	65
10	CuI	NaOH (4)	*t*BuOH	100	0	96
11	CuI	NaOH (4)	*t*BuOH	80	17	73
12	CuI	NaOH (4)	DMF	100	39	32
13	CuI	NaOH (4)	DMSO	100	21	25
14[c]	CuI	NaOH (4)	*t*BuOH	100	0	93
15	None	NaOH (4)	*t*BuOH	100	47	0

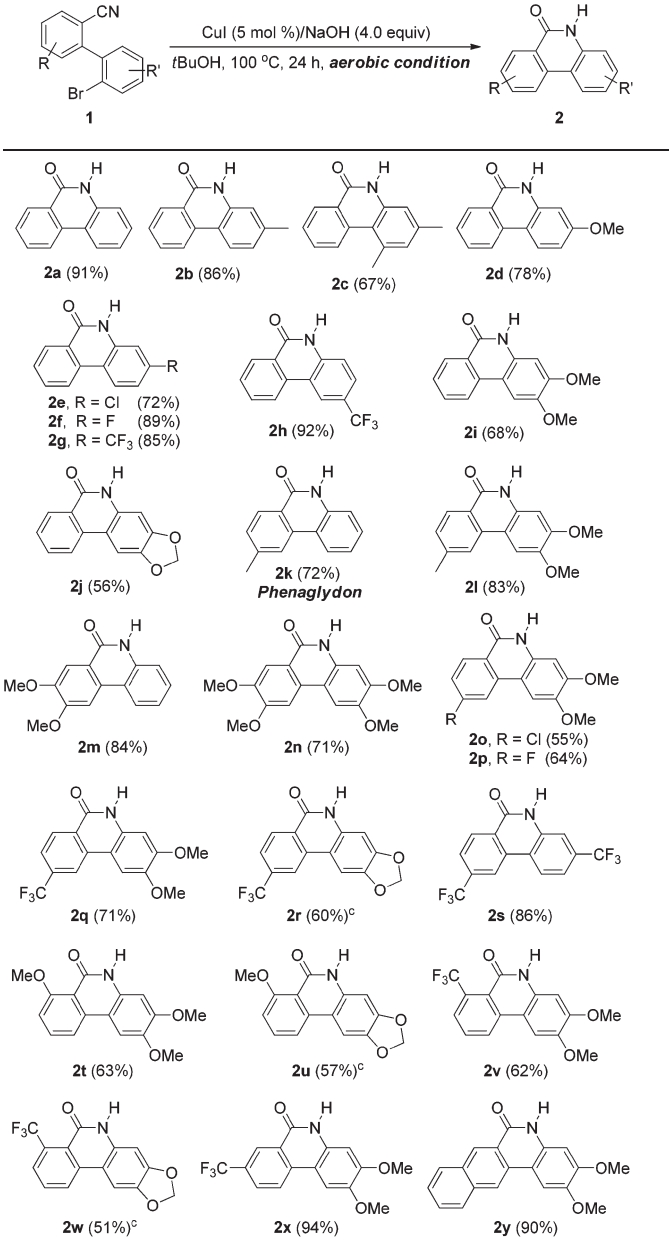
[a] Reactions were carried out using 0.1 mmol (1.0 equiv.) 2′-bromo-[1,1′-biphenyl]-2-carbonitrile (**1a**) with 5 mol% [Cu] and base (*n* equiv.) in 1.0 mL solvent at *T* °C for 24 h. [b] ^{1}H NMR yield based on internal standard mesitylene. [c] Under N_2.

desired product **2a** in lower yield. It was found that the amount of base significantly affected the yield of **2a**, and 4.0 equiv. of NaOH provided the best yield for this cyclization reaction (entry 8). Some unidentified compounds and biphenylamide were detected when the temperature was increased to 140 °C (entry 9). However, only desired product **2a** was obtained when the reaction temperature was decreased to 100 °C (entry 10).

The effect of solvent was investigated as well, and it was found that only highly polar solvents such as DMF and DMSO allowed the reaction to proceed successfully (entries 12 and 13). However, the substrate **1a** could be fully converted only when using *t*BuOH as solvent. In addition, there was no significant difference when running the reaction under nitrogen atmosphere or under air (entry 14). Moreover, the present cyclization reaction could not afford any desired product **2a** without a copper source (entry 15).

The copper-catalyzed cyclization reaction was successfully extended to various substrates (**1**), and the results are listed in Table 2. The reaction required at least 24 h to fully consume the substrates (**1**). As indicated, the reaction worked well for various substrates and both electron-donating and electron-withdrawing substituents on the aryl bromide moiety were well tolerated to give the corresponding products in moderate to good yields (**2a–2j**). Substituents *para* to the bromide (**2h–2j**) dramatically affected cyclization. Thus, a substrate with an electron-withdrawing group provided a higher yield of the corresponding product (**2h**) than those with an electron-donating group (**2i**, **2j**). We frequently detected a small amount of

Table 2 Scope of phenanthridinones[a,b]



[a] Reactions were carried out using 0.5 mmol (1.0 equiv.) substrate **1** with 5 mol% CuI, 4.0 equiv. NaOH in 5.0 mL *t*BuOH at 100 °C for 24 h. [b] Isolated yield. [c] 36 h.

the corresponding 2-bromobiarylamide for substrates with an electron-donating group on the aryl bromide moiety, which caused lower yields of the desired products (**2c**, **2d**, **2i** and **2j**). Substituents on the benzonitrile moiety were also well tolerated (**2k–2y**); however, the yields of the desired products were not only decided by the substituents on the benzonitrile moiety but also by the substituents on the aryl bromide moiety. When hydrophilic substituents such as methoxy group, chloride or fluoride were introduced into the phenanthridinones, the yields of the desired products were generally

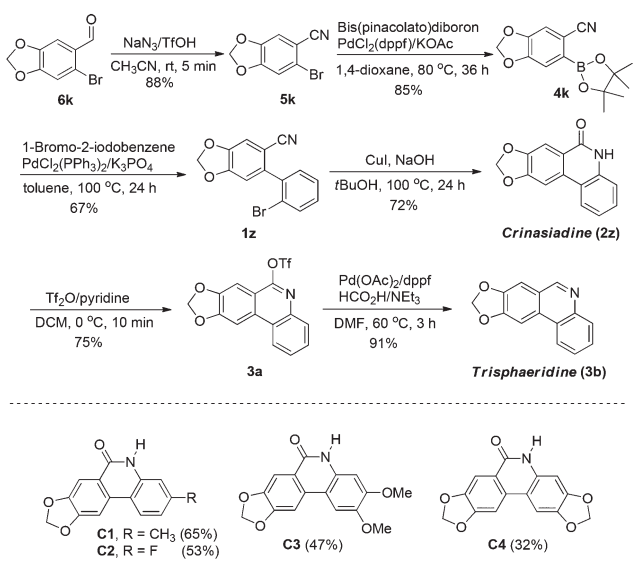
lower (**2n**, **2o**, **2p**, **2q** and **2r**). This is probably due to the partial solubility of the products in water during the extraction. It is noteworthy that product **2k** is a natural alkaloid known as phenaglydon, which has been isolated from the lipophilic leaf extract of *Glycosmis cyanocarpa* (Rutaceae).[20]

Reactions for substrates with a substituent *ortho* to the nitrile group (**2t**, **2u**, **2v** and **2w**) did not go to completion even after a longer reaction time. The *ortho* substituents would retard the addition of hydroxide to nitrile and reduce the yields of the corresponding products. Substrates with a *meta* CF_3 group on the benzonitrile moiety and with a naphthylnitrile moiety were also well tolerated to afford the corresponding products **2x** and **2y** in excellent yields. Substrates containing a picolinonitrile moiety or an electrophile such as a ketone group were not tolerated and the reactions provided messy crude spectra.

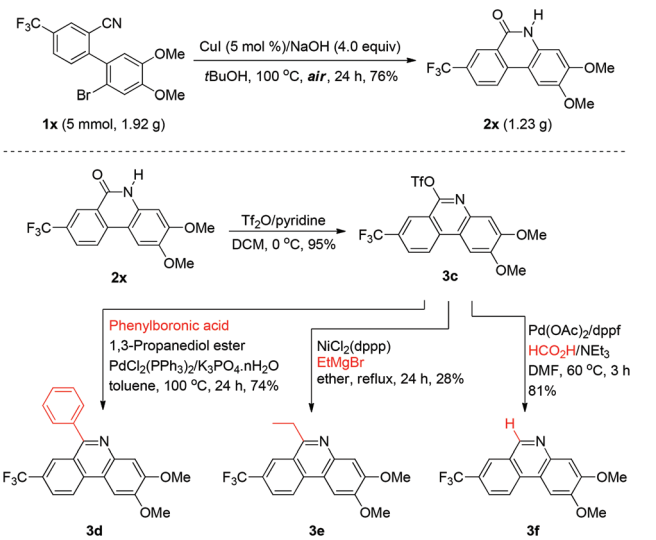
In order to extend the application of the present method, we selectively synthesized two natural alkaloids crinasiadine and trisphaeridine by using our developed protocol as the key step (Scheme 1). These two natural alkaloids represent the basic skeletons of the *Amaryllidaceae* alkaloids, which appear in a wide range of natural alkaloids and bioactive compounds. Our synthetic route began from a commercially available compound **6k**. Transformation of the aldehyde to nitrile and the subsequent Suzuki coupling reaction provided the substrate **1z**. Under the standard conditions of the present copper catalysis, **1z** was then converted to crinasiadine **2z** in 4 steps with 36% overall yield. Further transformation of **2z** to its corresponding phenanthridine afforded another natural alkaloid trisphaeridine **3b** with two more steps and 25% overall yield. Conversion of **2z** or **3b** to other natural alkaloids can be easily achieved by N-alkylation. For example, N-methylation of **2z** and **3b** can lead to other two natural alkaloids *N*-methylcrinasiadine[21] and bicolorine.[22] In addition, more complicated crinasiadine analogues (**C1**, **C2**, **C3** and **C4**) could be synthesized by this pathway in moderate to good yields.

The present methodology could be conducted for gram-scale synthesis as well. As shown in Scheme 2, conversion of **1x** to **2x** under the standard conditions was carried out on a 5 mmol scale with 76% isolated yield, which implied the potential applications in industry. We also synthesized variously poly-substituted phenanthridine derivatives *via* formation of the corresponding triflate compound **3c** as an important building block in excellent yield, and various 6-substituents could be introduced into the phenanthridine through palladium or nickel catalytic coupling reactions. 6-Aryl and 6-alkyl phenanthridines could be respectively afforded by Suzuki and Kumada type coupling reactions, and 6-*H*-phenanthridine could be provided by palladium catalyzed reduction with formic acid. Thus, the 6-phenylphenanthridine (**3d**), 6-ethylphenanthridine (**3e**) and 6-*H*-phenanthridine (**3f**) were successfully generated in 74%, 28% and 81% yields, respectively.

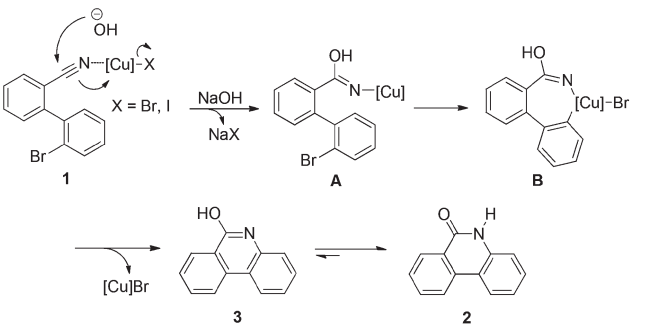
Although a more detailed study might be required to fully understand the mechanism of this copper-catalyzed annulation, a tentative pathway can be proposed according to the above results and previous report (Scheme 3).[19b] Thus, the



Scheme 1 Syntheses of crinasiadine, trisphaeridine and analogues of crinasiadine.



Scheme 2 Application to large-scale synthesis and syntheses of various phenanthridines.



Scheme 3 Proposed mechanism.

catalytic reaction is likely to be initiated by the coordination of the nitrile on compound **1** to a Cu(I) complex, which accelerates the following nucleophilic addition by hydroxide to form complex **A**. The oxidative addition of complex **A** in an intramolecular manner then occurred to generate Cu(III) species (complex **B**). The subsequent reductive elimination provides compound **3** and regenerates the Cu(I) species. Tautomerization of **3** affords the desired product **2**.

Conclusions

In conclusion, we have developed a novel method for the copper-catalyzed cascade reaction of C–O and C–N bond coupling. This method efficiently provides poly-substituted (NH)-phenanthridinones in moderate to good yields with tolerance of a wide variety of substrates. In addition, this method could be also applied to synthesize three natural alkaloids in a short number of steps with good overall yields. Moreover, conversion of the (NH)-phenanthridinone to the corresponding phenanthridines with various 6-substituents was carried out as well. Further studies to explore the possibility to extend the applications of this catalytic system are currently underway.

Experimental

General procedure for the copper-catalyzed cyclization

To a screw-capped vial (10 mL) were added CuI (0.025 mmol, 4.8 mg, 5 mol%), NaOH (2.0 mmol, 80 mg, 4.0 equiv.), and substrate **1** (0.5 mmol, 1.0 equiv.) in *t*BuOH (5 mL). The vial was then sealed with a cap and allowed to stir at 100 °C for 24 h. The crude reaction mixture was diluted with ethyl acetate (20 mL) and H_2O (10 mL). The mixture was then kept stirring at 70 °C for 30 min then the aqueous layer was removed and the organic layer was concentrated *in vacuo*. The residue was allowed to quickly flow through a short flash column chromatography by using ethyl acetate as eluent and then concentrated *in vacuo*, following washed by CH_2Cl_2 to provide the pure product. Products **2** were obtained according to this procedure.

Acknowledgements

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